

General

Guideline Title

Palliative radiotherapy: brain metastases.

Bibliographic Source(s)

Palliative Radiotherapy Working Group. Palliative radiotherapy: brain metastases. Edmonton (AB): CancerControl Alberta; 2014 Aug. 11 p. (Clinical practice guideline; no. RT-001). [54 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Health Services, Cancer Care. Palliative radiotherapy. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2010 Jul. 20 p. (Clinical practice guideline; no. PAL-001). [127 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Summary of Recommendations

Solitary

- Neurosurgery should be consulted for patients with a solitary brain metastasis.
- For solitary brain metastasis, whole brain radiotherapy (WBRT) is recommended after surgery. If patients are ineligible for surgery, or complete excision was not achieved, stereotactic radiosurgery (SRS) plus WBRT should be considered.

Multiple

- For patients with up to four newly diagnosed brain metastases, WBRT can be considered with or without SRS boost.
- Consider best supportive care for those patients with multiple brain metastasis and poor prognosis.

Recurrent/Progressive

- Status of extracranial disease burden, interval since initial treatment, initial treatment modalities, performance status, symptom burden, co-morbidities, prognosis and patient wishes should guide treatment decisions.

Recommendations for a Solitary Brain Metastasis

1. A neurosurgical opinion is strongly recommended for excision of a single brain metastasis, especially if it is larger than 3-4 cm, if patients have a good performance status (PS) and minimal, no, or controlled extra-cranial disease, especially in the absence of pathologic confirmation of malignancy. Surgical resection followed by post-operative WBRT is associated with a survival benefit over WBRT alone (Souchoon et al., 2010; Tsao et al., 2005; Lohr et al., 2001; Patchell et al., 1990; Noordijk et al., 1994; Patchell et al., 1998; Kalkanis et al., 2010). Post-operative WBRT reduces the risk of local and in-brain recurrence, increases the duration of functional independence, and decreases the likelihood of death secondary to neurological causes (Tsao et al., 2005; Lohr et al., 2001; Patchell et al., 1990; Noordijk et al., 1994; Patchell et al., 1998; Gaspar et al., 2010; Hart et al., 2005; Mintz et al., 2007). In a recently reported phase III trial in patients with one to three brain metastases from solid tumours, 199 patients post-SRS and 160 post-resection were randomized between observation and WBRT. There were no significant differences in overall survival (OS) or time to deterioration of PS, but WBRT significantly decreased 2 year local and distant in-brain relapse as well as rate of neurologic death after both modalities (Kocher et al., 2011).
2. In those not eligible for surgery or after incomplete excision, SRS should be considered in patients with one brain metastasis smaller than 4 cm in an appropriate location, good PS, and minimal, no or controlled extra-cranial disease. The combination of SRS and WBRT improves local control over WBRT alone and may improve survival in patients with a solitary brain lesion (Souchoon et al., 2010; Mintz et al., 2007; Andrews et al., 2004; Aoyama et al., 2006; Mehta et al., 2005; Muacevic et al., 2008; Linskey et al., 2010). SRS may be delivered either up front (Tsao et al., 2005) or subsequent to WBRT as a boost. A phase III trial of 199 patients post-SRS and 160 post-resection of 1 to 3 metastases from solid tumours randomized participants between observation and WBRT. There were no significant differences in OS or time to deterioration of PS. WBRT significantly decreased 2 year local and distant in-brain relapse as well as rate of neurologic death after both modalities (Kocher et al., 2011).
3. An alternative treatment option is surgery followed by SRS or radiotherapy (RT) directed to the resection cavity alone; however, supporting data is limited (Tsao et al., 2012). There is no convincing evidence that use of SRS in this setting improves outcomes in comparison to conventional external beam RT (Akhtar et al., 2012).
4. For a single metastasis <3-4 cm, SRS alone may be delivered (Tsao et al., 2012) but is not considered standard of care. However, in certain clinical situations where surveillance and salvage therapy are readily accessible, this may be an option (Mehta et al., 2005; Linskey et al., 2010).
5. In patients not eligible for surgery or SRS, WBRT alone is associated with an improvement in median survival compared to no treatment or best supportive care (BSC) with steroids (Weissman, 1988; Diener-West et al., 1989).
6. No strong evidence supports a specific WBRT dose fractionation schedule, with generally equivalent symptomatic improvement, median time to progression, and median survival for all regimens (Rodrigues et al., 2011; Borgelt et al., 1980; Kurtz et al., 1981). A meta-analysis of 27 publications reported no significant differences in mortality, symptom control, or neurological improvement with altered-dose compared to standard fractionation schedules (Tsao et al., 2005). Partial brain dose escalation has not proved clinically useful to date (Tsao et al., 2005; Gaspar et al., 2010; Sause et al., 1993).
7. In terms of toxicity, a WBRT dose of 30 Gy/10 may be associated with less late neuromorbidity in select long-term survivors and should be considered in patients with good PS and/or in the setting of planned SRS boost (Mintz et al., 2007). Prospective and retrospective studies have suggested moderate deterioration in global quality of life, physical/motor function, and communication ability three months after WBRT (Weissman, 1988; Diener-West et al., 1989; Steinmann et al., 2012). Adding WBRT to SRS may be associated with a decline in learning and memory by four months compared to patients receiving SRS alone (Chang et al., 2009). However, potential side effects of WBRT must be weighed against the likelihood of morbidity resulting from in-brain recurrence/progression if WBRT is not administered. Potential benefits and side effects of WBRT should be discussed with patients.
8. Although studies investigating chemotherapy following WBRT suggest improved intracranial response, they also generally report increased toxicity and no statistically significant survival benefit, and are therefore not currently recommended outside of a clinical trial setting (Mehta et al., 2010).
9. The use of radiosensitizers is not recommended outside of a clinical trial setting. The RTOG 7916 trial utilizing misonidazole and two subsequent systematic reviews have reported no survival benefit from the addition of radiosensitizers to WBRT (Tsao et al., 2005; Komarnicky et al., 1991; Viani et al., 2009).
10. Patients with an expected very poor prognosis should be considered for BSC alone (Tsao et al., 2012).

Recommendations for Multiple Brain Metastases

11. For patients with up to four newly diagnosed brain metastases each smaller than 4 cm, there is strong evidence from two large randomized controlled trials and several systematic reviews and meta-analyses that SRS boost after WBRT significantly improves local control and PS compared with WBRT alone (Tsao et al., 2012; Souchoon et al., 2010; Andrews et al., 2004; Mehta et al., 2005; Linskey et al., 2010; Kondziolka et al., 1999). There may also be a survival advantage for certain subgroups of patients, although the evidence is limited (Linskey et al., 2010; Wang et al., 2002; Sanghavi et al., 2001). In a recently reported phase III trial, 199 post-SRS and 160 post-resection patients

who had one to three brain metastases from solid tumours were randomized between observation and WBRT. There were no significant differences in OS or time to deterioration of PS, but WBRT significantly decreased 2 year local and distant in-brain relapse as well as rate of neurologic death after both modalities (Kocher et al., 2011).

12. WBRT alone is associated with an improvement in median survival compared to steroids alone.
13. Following resection of one or more brain metastases causing significant mass effect, postoperative WBRT may be considered (Tsao et al., 2012).
14. No strong evidence supports a specific WBRT dose fractionation schedule, with generally equivalent symptomatic improvement, median time to progression, and median OS reported for all regimens (Borgelt et al., 1980; Kurtz et al., 1981; Sanghavi et al., 2001; Rades et al., "Dose escalation," 2007; Rades et al., "Reduction," 2007; Murray et al., 1997). Partial brain dose escalation and altered fractionation have not proved clinically useful to date; a 2005 meta-analysis reported no significant differences in mortality, symptom control, or neurological improvement in nine trials of altered-dose fractionation schedules (Tsao et al., 2012; Tsao et al., 2005; Gaspar et al., 2010; Sause et al., 1993).
15. In terms of toxicity, a WBRT dose of 30 Gy/10 fractions may be associated with less late neuromorbidity in select long term survivors, and should be considered in patients with good PS and/or in the setting of planned SRS boost (Tsao et al., 2012; Gaspar et al., 2010).
16. SRS alone is not considered standard of care, but in certain clinical situations where surveillance and salvage therapy are readily accessible, treatment with SRS alone may be an option (Mehta et al., 2005; Linskey et al., 2010).
17. Patients with an expected very poor prognosis should be considered for BSC alone (Tsao et al., 2012).
18. In the setting of one or more inoperable brain metastases from non-small cell lung cancer (NSCLC), there is some interim randomized phase III data which suggests that treatment with WBRT plus BSC may not offer a measurable improvement in quality adjusted life years over BSC alone in patients median age 67 years, with 50% of patients having a Karnofsky performance status <70 (Langley et al., 2013).
19. WBRT plus chemotherapy is associated with increased toxicity and no significant survival benefit over WBRT alone. Therefore, WBRT in combination with chemotherapy cannot be recommended outside of a clinical trial setting. Nevertheless, some evidence has demonstrated promising results when chemotherapy is used in combination with WBRT, as it may lead to improved in-brain responses and increased time to neurological progression, particularly for patients with breast or non-small cell lung cancer brain metastases (Mehta et al., 2010; Langer & Mehta, 2005; Walbert & Gilbert, 2009).
20. The RTOG 7916 trial reported no survival benefit associated with the addition of the radiosensitizer misonidazole to WBRT (Komarnicky et al., 1991). Since that trial, limited evidence suggests that motexafin gadolinium may increase time to neurological progression for intent-to-treat patients with NSCLC-associated brain metastases treated with WBRT (Mehta et al., 2009), however, this has not been confirmed by additional studies. Therefore, the use of radiosensitizers is not recommended outside of a clinical trial setting (Knisely et al., 2008).

Recommendations for Recurrent or Progressive Brain Metastases

21. No standard treatment has been established (Souchoy et al., 2010). The choice of therapeutic approach will depend on the status of any extracranial disease, interval since initial treatment, initial treatment modalities, PS, symptom burden, co-morbidities, prognosis and patient wishes.
22. Although there is a lack of evidence for the use of SRS in the salvage setting, this may be an option for select patients with one to four recurrent or progressive brain metastases, good PS, and minimal, no, or controlled extra-cranial disease (Mehta et al., 2005).
23. Resection of one or more brain metastases causing significant mass effect, or salvage partial brain external beam RT, may be considered on a case-by-case basis.
24. Repeat WBRT is an option in highly selected patients with minimal, no or controlled extracranial disease and should be considered on a case-by-case basis in the absence of other treatment options (Son et al., 2012; Sadikov et al., 2007). Patients who may benefit most from re-irradiation include those with a survival greater than three to six months after initial WBRT, new neurological symptoms, and a good PS (Morris, 2000; Ammirati et al., 2010). Several small retrospective studies have examined the utility of repeat WBRT in recurrent brain metastases. Early data suggests improvement in OS if reirradiation dose is >20 Gy but there is no standard dose-fractionation in use. Median survival after re-irradiation was 2.8-5.2 months, with up to 68% of patients experiencing symptomatic improvement (Son et al., 2012; Sadikov et al., 2007; Abdel-Wahab et al., 1997; Akiba et al., 2012; Ozgen et al., 2013; Scharp et al., 2014; Wong et al., 1996).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Advanced cancer with brain metastases

Guideline Category

Management

Treatment

Clinical Specialty

Neurological Surgery

Neurology

Oncology

Radiation Oncology

Radiology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To reduce practice variations in radiotherapy (RT) for brain metastases where the evidence exists to support a pattern of practice

Target Population

Adult patients, with a single or multiple brain metastases, arising from cancer of any histology, excluding germ cell tumours and hematologic malignancies

Interventions and Practices Considered

1. Neurosurgical opinion
2. Post-operative whole brain radiotherapy (WBRT)
3. Stereotactic radiosurgery (SRS)
4. WBRT/SRS combination therapy
5. Salvage SRS in selected cases
6. Repeat WBRT in highly selected patients
7. Consideration of fractionation schedule
8. Best supportive care (BSC)
9. Resection or partial brain external beam radiotherapy (RT)

Note: The following interventions were considered but not recommended or there was no strong evidence to support a recommendation:

Altered fractionation and partial brain dose escalation

Use of radiosensitizers and chemotherapy post-WBRT outside of a clinical trial setting

WBRT/BSC combination

Major Outcomes Considered

- Survival
- Local control
- Distant in-brain control
- Duration of functional independence
- Neurocognitive status
- Improvement in presenting symptoms
- Toxicity events
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Guideline Questions

What are the recommended strategies for the management and treatment of adults with:

- A newly diagnosed solitary brain metastasis?
- Newly diagnosed multiple brain metastases?
- Progressive or recurrent brain metastases?

Search Strategy

For the 2014 update, the following electronic databases were searched (July, 2010 to January, 2014): PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Google Scholar. The search strategy involved a combination of medical subject (MeSH) terms and text words.

Articles were excluded if they: had a non-English abstract, were not available through the library system, were case studies involving less than 10 patients, or involved pediatric patients. The references cited in articles identified through the formal searches were also scanned for additional sources. An environmental scan of the literature was also performed.

A search for new or updated clinical practice guidelines published from July, 2010 to April, 2013 was also conducted, and yielded published guidelines by the following organizations: American Society for Radiation Oncology (ASTRO), National Cancer Institute, National Institute for Health and Care Excellence (NICE), and European Society for Medical Oncology.

Search Terms

(Palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields]OR "radiotherapy"[MeSH Terms]) AND ("brain"[MeSH Terms] OR "brain"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastases"[All Fields])).

Articles were excluded if they: had a non-English abstract, were case studies involving less than 10 patients, or involved pediatric patients.

Number of Source Documents

- Number studies identified: 103
- Number of studies included: 19

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the Knowledge Management (KM) Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (<http://www.agreetrust.org>) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, Guideline Utilization Resource Unit (GURU) does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The original guideline was developed in 2008 by the clinical leaders of the Fast Track Palliative Radiotherapy Clinic for Bone Metastases in Calgary and the Palliative Radiation Oncology program (originally called the Rapid Access Palliative Radiotherapy Program) in Edmonton, with input from provincial radiation oncologists. For the 2010 updates, evidence was selected and reviewed by a working group comprised of radiation oncologists from Alberta Health Services – CancerControl Alberta and a Knowledge Management (KM) Specialist from the Guideline Resource Unit. In 2014, the larger guideline was converted into several smaller guidelines. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook (see the "Availability of Companion Documents" field).

Formulating Recommendations

The working group members formulate the guideline recommendations based on the evidence synthesized by the KM Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed above, the working group members may decide to adopt the

recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members will be explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Guideline Review and Approval

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it will be sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Director of Provincial Clinical Teams.

Evidence Supporting the Recommendations

References Supporting the Recommendations

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Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of palliative radiotherapy to improve outcomes in patients with brain metastases

Potential Harms

In terms of toxicity, a whole brain radiotherapy (WBRT) dose of 30 Gy/10 may be associated with less late neuromorbidity in select long-term survivors and should be considered in patients with good performance status (PS) and/or in the setting of planned stereotactic radiosurgery (SRS) boost. Prospective and retrospective studies have suggested moderate deterioration in global quality of life, physical/motor function, and

communication ability three months after WBRT. Adding WBRT to SRS may be associated with a decline in learning and memory by four months compared to patients receiving SRS alone. However, potential side effects of WBRT must be weighed against the likelihood of morbidity resulting from in-brain recurrence/progression if WBRT is not administered. Potential benefits and side effects of WBRT should be discussed with patients.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present and review the guideline at relevant local and provincial tumour team meetings and weekly rounds.
- Include a link to the guideline in other relevant disease-specific clinical practice guidelines published by Alberta Health Services – CancerControl Alberta.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services – CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Palliative Radiotherapy Working Group. Palliative radiotherapy: brain metastases. Edmonton (AB): CancerControl Alberta; 2014 Aug. 11 p. (Clinical practice guideline; no. RT-001). [54 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2010 Jul (revised 2014 Aug)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

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CancerControl Alberta

Guideline Committee

Palliative Radiotherapy Working Group

Composition of Group That Authored the Guideline

Not stated

Financial Disclosures/Conflicts of Interest

Participation of the Alberta Health Services – CancerControl Alberta radiation oncologists in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some of the individuals involved in the development of this guideline are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Health Services, Cancer Care. Palliative radiotherapy. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2010 Jul. 20 p. (Clinical practice guideline; no. PAL-001). [127 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the [Alberta Health Services Web site](#) .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2013 Jan. 5 p. Electronic copies:

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 10, 2012. The information was verified by the guideline developer on March 30, 2012. This summary was updated by ECRI Institute on July 3, 2014 following the U.S. Food and Drug Administration advisory on Epidural Corticosteroid Injection. This summary was updated by ECRI Institute on December 19, 2014. The updated information was verified by the guideline developer on January 12, 2015.

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